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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/559,764	04/27/00	FLODGAARD H	5694.200-US

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/559,764	Applicant(s) FLODGAARD ET AL.	
	Examin r Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *7-11 and 15-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 and 7* .
18) ☒ Interview Summary (PTO-413) Paper No(s). 7 .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. The instant application is in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

2. Applicant's election of Group II (antibody antagonist of HBP) in Paper No. 8 with a species election of SIRS is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Election of an antibody antagonist of HBP was confirmed with Cheryl H. Agris on 4/9/01, as indicated in the attached Interview Summary.

Claims 7-11 and 15-42 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions or species.

Claims 1-6 and 12-14 *are under consideration in the instant application.*

3. Priority: Provisional applications 60/12,748 (4/29/99) and 60/157,384 (10/1/99) each appear to provide adequate written support for instant claims 1-6. However, neither an antibody to the specific epitope of a prekallikrein-H-kininogen complex nor a human antibody appear to have adequate written support in either provisional application; thus claims 12-14 are considered to have the priority date of the instant application (4/27/00).

Applicant is invited to point to clear support for the claimed subject matter in each provisional application; if Applicant disagrees with the Examiner's analysis.

4. Applicant's IDS, filed 11/9/00 (Paper No. 7), is acknowledged.

Applicant is required to provide a full citation including a journal source and publication date for the Peterson et al. and Heinzelmann et al. references.

5. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

8. Claims 1-6 and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 and 12-14 are indefinite in that they only describe the compositions of interest by the arbitrary protein name "HBP". While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein. For example, others in the field may isolate the same protein and give such an entirely different name (e.g., see Rasmussen et al. FEBS Lett. 390:109-112 1996). In addition, other proteins are known in the art that also bind to heparin and therefore constitute "heparin binding proteins", e.g., collagen. Applicant should particularly point out and distinctly claim the HBP by claiming characteristics associated with the protein (e.g. a SEQ ID NO:, , etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and of what the composition is made.

In addition, claims 1-6 and 12-14 are indefinite and ambiguous in the recitation of the abbreviation "HBP" rather than "heparin binding protein" because an abbreviation can indicate a number of entities. Applicant should amend the claims to recite the proper name of the claimed molecules.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims recite a monoclonal antibody that binds to at least one epitope of HBP, wherein said epitope binds to prekallikrein-H-kininogen complex and activates release of bradykinin.

While Applicant's disclosure appears to support a role for HBP in the release of bradykinin from H-kininogen after cleavage by kallikrein (e.g., the Examples on pages 44-48 of the specification), the disclosure does not appear to enable the actual binding of an epitope of HBP to the prekallikrein-H-kininogen complex, and therefore does not appear to enable a monoclonal antibody to the proposed epitope of HBP.

The state of the art clearly recognizes a role for HBP in inflammation (e.g. reviewed in Pereira J. Leukocyte Biol 57:805-812, 1995). For instance, Pereira teaches that the protein CAP37, which as noted supra is the same protein as the HBP of the instant invention, is involved in inflammation by virtue of multiple functions: binding of endotoxin (LPS/lipid A), direct microbicidal activity, and the recruitment of cells to the inflammatory site (see entire document, especially "Discussion" on page 810). Applicant provides data supporting a role for HBP in mediation of inflammation, as assessed primarily by monitoring changes in endothelial cell (EC) permeability.

However, although Applicant provides evidence that blocking HBP (by binding to aprotinin) or blocking various steps in the direct activation of bradykinin inhibits the HBP-induced increase in EC permeability; it is unpredictable as to whether HBP and the prekallikrein-H-kininogen complex directly interact (i.e., that an epitope of HBP specifically binds the prekallikrein-H-kininogen complex), or whether intermediaries exist that mediate the observed effect. In the absence of objective evidence or working examples indicating that an epitope on HBP specifically binds the prekallikrein-H-kininogen complex; the skilled artisan would not reasonably predict that an antibody that specifically binds to an epitope of HBP, wherein said epitope binds the prekallikrein-H-kininogen complex, could be used to as an HBP antagonist in the prevention or treatment of any disorder. Before the skilled artisan would have a reasonable expectation of successfully producing a monoclonal antibody to the epitope; the skilled artisan would first have to ascertain whether or not an HBP epitope that binds the prekallikrein-H-kininogen complex exists. Thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

11. Claims 1-6 (and 12-14 if an epitope of HBP that binds the prekallikrein-H-kininogen complex is subsequently shown to be enabled) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for at least a method of reducing or inhibiting an inflammatory disorder mediated at least in part by bradykinin release, does not reasonably provide enablement for a method of preventing or treating systemic inflammatory response syndrome or other disorders which involve multiple mediators in addition to bradykinin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. A person of skill in the art would not be able to prevent or treat a disorder resulting from the release of bradykinin, as recited in the claims.

Although bradykinin is known to reproduce some of the characteristic associated with the inflammatory state, such as vasodilation and pain (e.g., reviewed in Colman et al., Blood 90:3819-3843 1997) the disorders recited by Applicant can involve many additional mediators. For example, systemic inflammatory response syndrome is itself a collection of conditions associated with inflammation. As reviewed by Grunfield et al. (US Pat. No. 5,660,826), systemic inflammatory response syndrome encompasses such conditions as sepsis or even the response to multiple trauma (e.g., "Background of the Invention", especially 1st paragraph). Grunfield goes on to note that, at least with respect to the specific systemic inflammatory response syndrome condition of sepsis, many of the toxic effects are mediated by cytokines, hormones, and other small molecules (e.g., bridging paragraph columns 1 and 2). Further, Grunfield et al. conclude that treatments will need to combine a plurality of approaches in view of the large cascade of pro-inflammatory cytokines released (e.g., see especially column 2 at line 4-13). Therefore, it is highly unpredictable that a single therapeutic modality, such as administering an antagonist of HBP, would be sufficient to treat systemic inflammatory response syndrome.

In addition, although in some of the conditions encompassed by the term systemic inflammatory response syndrome the timing of the insult/trigger is known (e.g., in surgery induced trauma), in other condition encompassed by this term the timing is not known (e.g., sepsis). The skilled artisan would expect that a method of preventing a disorder in which the timing of the insult/trigger is not known would be highly unpredictable. Therefore, the skilled artisan would not reasonably expect that the invention could be used in preventative methods commensurate with the scope of the conditions recited in the instant claims.

In view of the unpredictability associated both with methods of treating and with methods of preventing the full scope of the recited disorders; the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> *(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.*

13. Claims 1 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Oppenhelm et al. (US Pat. No. 5,837,247, see entire document), as evidenced by Rasmussen et al. (FEBS Lett. 390:109-112 1996, see entire document).

Oppenhelm et al. teach a method for reducing or inhibiting an inflammatory disorder in a subject comprising administering an antagonist of CAP37/HBP (see entire document; e.g., column 2, especially lines 57-67); wherein the antagonist is a monoclonal antibody to CAP37/HBP (e.g., columns 9-10, especially bridging paragraph).

CAP37 and HBP are the same protein, as evidenced by Rasmussen et al. (e.g., "Introduction").

Systemic inflammatory response syndrome encompasses multiple inflammatory disorders; thus the claim is anticipated (see MPEP 2131.02).

In addition, Applicant is reminded that when a claim recites using an old composition or structure (e.g. an HBP-specific antibody) and the use is directed to a result or property of that composition or structure (e.g., effective to decrease release of bradykinin), then the claim is anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant is further reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property, such as the inherent decreased release of bradykinin in response to administering an antibody to HBP. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency.

Finally, no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitation of decreasing release of bradykinin would be an inherent property of the referenced anti-CAP37/HBP antibody.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oppenhelm et al. (US Pat. No. 5,837,247) as evidenced by Rasmussen et al. (FEBS Lett. 390:109-112 1996); in view of Grunfield et al. (US Pat No. 5,660,826).

The claims are drawn to dosages of administration of an HBP/CAP37 antagonist wherein the antagonist is an antibody.

Oppenhelm et al. as evidenced by Rasmussen et al. have been discussed supra.

Oppenhelm et al. do not explicitly teach the dosage of administration of the antibody inhibitor of HBP.

Grunfield et al. teach and claim a method comprising administering to a patient suffering from risk of systemic inflammatory response syndrome an effective amount of an antibody inhibitor wherein the antibody inhibitor is administered in the pharmaceutically effective amount of 1μg/kg to 10mg/kg (see entire document, especially claims 1 and 2). Grunfield et al. also teach that the dose is subject to a great deal of therapeutic discretion, and that higher doses may be needed (e.g., column 4, especially lines 23-37).

Given the teachings of Grunfield et al. with respect to dosages of administering antibodies for treating systemic inflammatory response syndrome conditions such as shock; it would have been obvious to the ordinary artisan at the time the invention was made to utilize similar dosages of antibodies to HBP, especially since the therapeutic use of anti-HBP antibodies taught by Oppenhelm et al. is for inhibiting inflammation. The ordinary artisan would have been motivated to utilize these similar dosages in light of the similarities of the therapeutic modality, an antibody, and the conditions treated. In addition, given these similarities, the ordinary artisan would have had a reasonable expectation that the effective dose of the antibody antagonist of HBP was similar to or encompassed by the range taught by Grunfield et al. Finally, the ordinary artisan would have been motivated to formulate the antibody composition in an amount of from about 10mg to 1g per unit dosage in order to provide sufficient quantities of the antibody preparation in a reasonably compact dosing. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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April 10, 2001

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